Clinical usefulness of endoscopic ultrasonography-guided fine-needle aspiration in the diagnosis and staging of lung cancer

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ABSTRACT

Lung cancer is the most common cause of cancer-related mortality in Singapore, and accurate staging of lung cancer is therefore of paramount importance. Several non-invasive and invasive modalities can be used to stage lung cancer. Endoscopic ultrasonography-guided fine-needle aspiration (EUS-FNA) is a safe procedure that is performed under conscious sedation and has a sensitivity of up to 90-98 percent in expert hands. In addition, nodal groups that are inaccessible by cervical mediastinoscopy (such as the aortopulmonary window lymph nodes) can be sampled by EUS-FNA. We present three cases in which EUS-FNA was used successfully to diagnose and stage lung cancer, thus avoiding surgery.

Keywords: cancer staging, endoscopic ultrasonography-guided fine-needle aspiration, endosonography, fine-needle aspiration, lung cancer, mediastinum

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INTRODUCTION

Carcinoma of the lung is the most common cause of cancer-related mortality in Singapore, accounting for 28.1% of all cancer deaths in males and 16.4% of all cancer deaths in females. Treatment strategies are largely based on two factors: firstly, histology (small cell versus non-small cell) and secondly, the absence or presence of mediastinal involvement or distant spread of the tumour. Patients without mediastinal involvement are potential candidates for surgical resection.[1,2] In some centres, patients with Stage IIIa disease (ipsilateral malignant mediastinal lymph nodes – N2) may be offered surgery after neoadjuvant chemoradiation. Those with Stage IIIb disease (contralateral malignant mediastinal lymph nodes – N3) are generally offered chemotherapy without surgery. Accurate staging therefore dictates management plans and guides prognosis. Accurate staging is also necessary in clinical trials comparing different chemotherapeutic agents.

Several modalities, which may be non-invasive or invasive, can be used to stage lung cancer. The most commonly-used modality is computed tomography (CT), which is non-invasive and easily available. However, CT is only able to characterise the size and location of lymph nodes. The sensitivity and specificity of CT in identifying malignant mediastinal lymphadenopathy is only around 70%.[2-4] CT-guided fine-needle aspiration (FNA) of the mediastinum is limited by surrounding bony and cardiovascular structures, and carries a risk of pneumothorax. Positron-emission tomography (PET) with 3-flurodeoxyglucose uses differing rates of glucose metabolism to distinguish between benign and malignant nodes. PET is non-invasive and has an accuracy of 85%.[5] However, it is plagued by a high positive rate which may deny patients a possible cure by surgery. It is also limited by false-negative results in tumours with low metabolic activity or in small nodes less than 1 cm in size.[6,7]

Invasive staging procedures are usually carried out to confirm a presumptive diagnosis of lung cancer, obtain tissue confirmation of the cell type, and to confirm the staging of the malignancy. Mediastinoscopy has long been considered the "gold standard" for the diagnosis and staging of mediastinal lymphadenopathy. However, mediastinoscopy is an invasive procedure which needs to be performed under general anaesthesia.[8] Nodal groups that cannot be sampled by standard cervical mediastinoscopy include the posterior subcarinal, inferior mediastinal and aortopulmonary window nodes.[9] The development of minimally invasive techniques offers increased patient safety as well as potential cost savings for the staging process. Bronchoscopy with transbronchial FNA of the subcarina and hilum, though safe and well-tolerated, is a blind procedure that has a low diagnostic yield of approximately 60%.[10] It also does not allow access to the aortopulmonary window or inferior mediastinal nodes.[11]

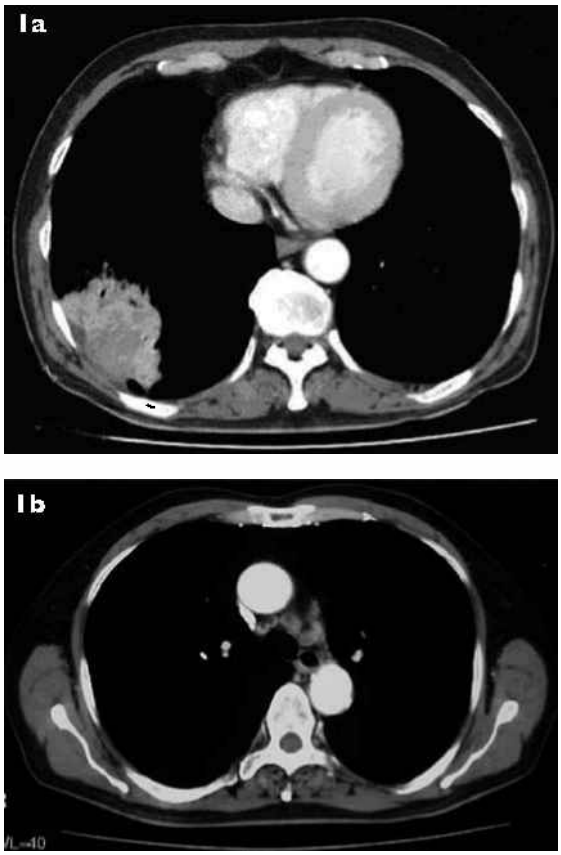

Fig. 1 Case 1. Axial CT images of the thorax show (a) a large mass in right lower lobe of the lung; and (b) enlarged lymph nodes in the aortopulmonary window.

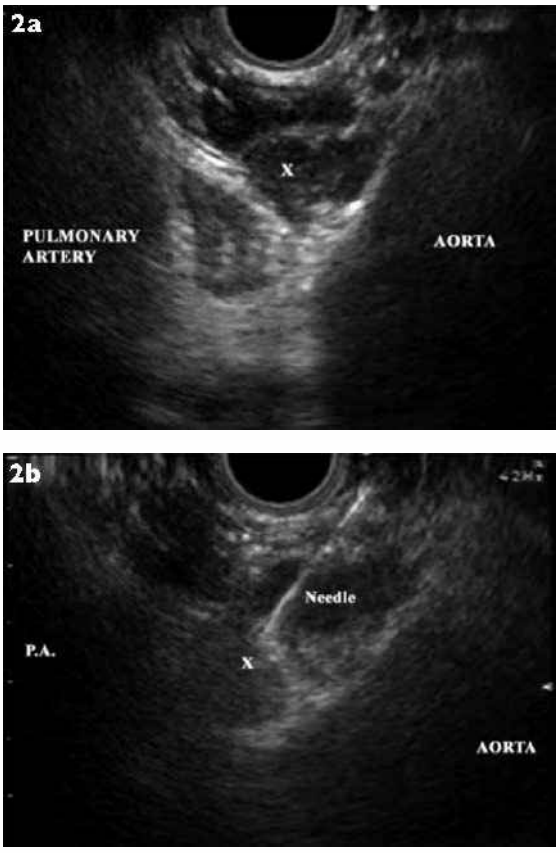

Fig 2. Case 1. Echoendoscope images show (a) enlarged aortopulmonary lymph nodes; and (b) EUS-FNA of aortopulmonary lymph node being performed using a 22-gauge needle.

Endoscopic ultrasonography (EUS) is a relatively new endoscopic technique involving the use of an endoscope with an ultrasound transducer at its tip. Endoscopy allows for placement of the ultrasound probe nearer organs of interest, providing high-resolution images. Suspicious extraluminal lesions can be biopsied under real-time US guidance. The addition of Doppler technology allows the identification of any intervening vascular structures, increasing the safety profile of EUS-FNA. Although originally developed for gastrointestinal lesions, EUS also provides an excellent view of the posterior mediastinum through the oesophageal wall, allowing for safe and accurate FNA of suspicious mediastinal nodes to be carried out under real-time US visualisation.[12] EUS-FNA is a minimally invasive procedure performed with the patient under conscious sedation. It is able to sample the posterior subcarinal, inferior mediastinal and aortopulmonary window nodes – the areas which are inaccessible by mediastinoscopy. The upper retroperitoneum can also be evaluated, especially the area around the coeliac trunk and the left adrenal gland.[13] EUS and EUS-FNA have become more available in Singapore in recent years. However, its use in the diagnosis and staging of lung cancer remains relatively under-utilised. In this report, we describe the use of EUS-FNA in three cases, demonstrating its ability to obtain tissue for the histological diagnosis of lung cancer as well as in confirming the mediastinal staging.

CASE REPORTS

Case 1

A 71-year-old Malay man was referred for lung cancer staging. CT of his thorax showed a lobulated spiculated mass in the periphery of the right lower lobe, with enlarged aortopulmonary and paratracheal lymph nodes (Fig. 1). CT-guided biopsy of the mass confirmed the presence of invasive adenocarcinoma. As the patient was potentially a surgical candidate, he was referred for EUS-FNA to further stage the disease. A curvilinear array echoendoscope (Olympus UC140P-AL5; Olympus, Singapore) was used to evaluate the mediastinum and to perform EUS-FNA. EUS confirmed the presence of aortopulmonary lymphadenopathy (Fig. 2a). Under real-time US visualisation, a 22-gauge needle (Wilson-Cook Medical Inc, Winston-Salem, NC, USA) was used to sample the lymph nodes in the aortopulmonary window (Fig. 2b). Three passes were

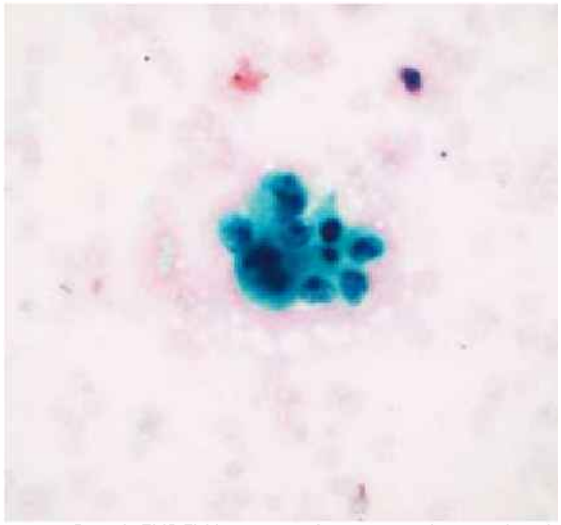

Fig. 3 Case 1. EUS-FNA specimen from aortopulmonary lymph node shows malignant cells with vesicular nuclei containing nucleoli (Papanicolau stain, ×60).

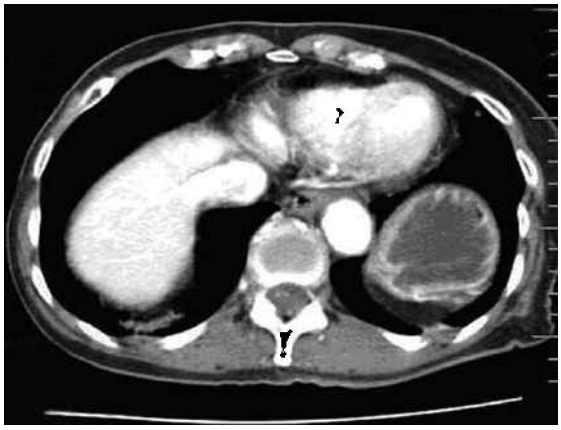

Fig. 4 Case 2. Axial CT image of the thorax shows a spiculated lung mass in the right lower lobe of the lung.

Fig. 5 Case 2. EUS-FNA specimen from a paratracheal lymph node shows immunostain positivity indicating a neuroendocrine origin (Synaptophysin stain, ×20).

made. All procedures were performed by a single endosonographer (CTS) who had performed more than 1,000 EUS procedures.

Two types of specimens were obtained: smears, which were prepared directly from the aspirate and centrifuged material from needle washings; and cell blocks. The smears were either air-dried and stained with Diff-Quik (DQ) or immediately put in alcohol and stained with Papanicolau. During each procedure of EUS-FNA, a cytopathologist was present to concurrently analyse DQ-stained smears, which were rapidly available. The cell blocks, which were fixed with formalin, were subsequently either stained with Haematoxylin and eosin, or special stains: periodic acid schiff, synaptophysin, mucicarmine, TTF-1 immunostains. Cytology obtained from the aortopulmonary lymph nodes revealed the presence of groups of malignant cells with features suggestive of a poorly-differentiated adenocarcinoma, rendering the patient inoperable (Fig. 3). He was subsequently referred for chemotherapy.

Case 2

A 77-year-old Chinese woman was referred to the surgical clinic for evaluation of recent weight loss. She was a non-smoker and did not have symptoms specific to any organ system. Chest radiograph showed a mass in the right lower zone. Subsequent CT of her thorax confirmed the presence of a spiculated mass in the right lower lobe (Fig. 4). Enlarged right paratracheal lymph nodes were also noted. CT of her abdomen revealed no lesion other than a small pancreatic cyst. The patient was referred for EUS-FNA to determine the nature of the paratracheal lymphadenopathy. EUS confirmed the presence of mediastinal lymphadenopathy. EUS-FNA of the paratracheal lymph nodes was performed using a 22-gauge needle. Four passes were made. The specimens obtained were processed as in Case 1. Abundant apoptosis and necrotic debris were noted. The tumour cells stained strongly for a synaptophysin and TTF-1 (Fig. 5). The features were those of a small cell carcinoma consistent with a lung primary. The patient was referred for chemotherapy.

Case 3

A 68-year-old Malay man with a 40-pack/year smoking history was admitted for left hip pain. Chest radiograph showed an opacity in the right lung, which was not present on the chest radiograph performed three years earlier. Sputum cytology did not yield any malignant cells. Subsequent CT of his thorax revealed a right upper lobe peripheral lesion on a background of bullous lung emphysema, as well as "cystic"-looking pretracheal and right hilar lymph nodes (Fig. 6). Radiological-guided

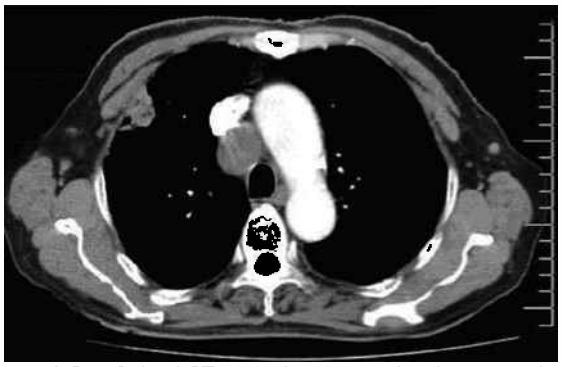

Fig. 6 Case 3. Axial CT image shows a peripheral mass in right upper lobe of the lung.

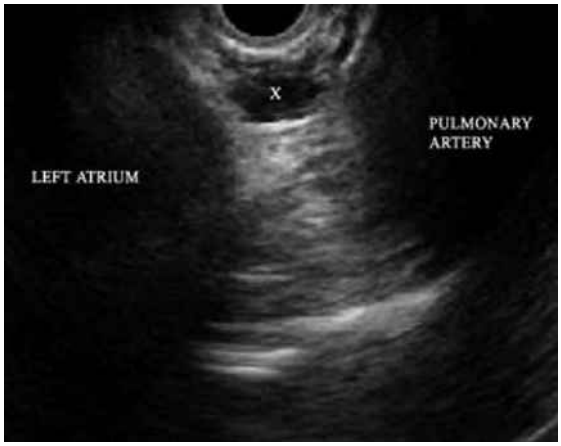

Fig. 7 Case 3. Echoendoscope image shows a subcarinal lymph node (x).

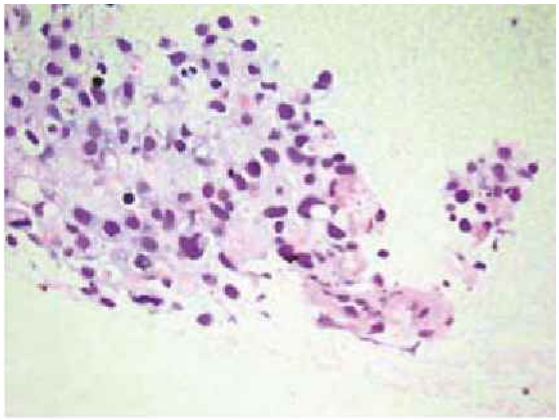

Fig. 8 Case 3. EUS-FNA specimen from subcarinal lymph node shows positivity of mucicarmine in the cytoplasm of malignant cells (Mucicarmine stain, ×40).

percutaneous biopsy of the lung lesion would carry a high risk of pneumothorax, given the emphysematous lung changes. Hence, the patient was referred for EUS-FNA to determine the nature of the paratracheal and right hilar lymphadenopathy, for both diagnostic and staging purposes. EUS revealed an enlarged lymph node just proximal to the subcarinal level (Fig. 7). EUS-FNA of the subcarinal lymph node was performed. Four passes were made. Cytological examination confirmed the presence of a moderately differentiated adenocarcinoma (Fig. 8). The patient was referred for chemotherapy as he had an inoperable disease.

DISCUSSION

Hippocrates once observed: "Extreme remedies are very appropriate for extreme diseases". A patient diagnosed with an "extreme disease" such as lung cancer, is faced not only with a dismal prognosis, but also the possibility of undergoing tumour resection via thoracotomy. Although this procedure causes significant morbidity, it also offers the patient the best chance for cure. When traditional preoperative staging methods are used, approximately 10% of operations for non-small cell lung cancer result in explorative thoracotomy without tumour resection, due to advanced mediastinal disease that is not detected preoperatively. Furthermore, early postoperative recurrent disease occurs in 25%–35% of apparently curative resections.[14] It is estimated that surgery is futile or unnecessary in up to 45% of patients who are operated on, as the disease is more advanced than assessed preoperatively. Since the success of surgery hinges on accurate staging, the development of methods that can more accurately stage lung cancer is of paramount importance.[15] Fritscher-Ravens et al compared CT, PET and EUS-FNA for identifying inoperable patients in a consecutive cohort of 79 potentially operable patients with suspected or proven lung cancer.[16] Each test was interpreted blinded with respect to the other tests. 39 patients were found to be inoperable (a 40th patient's inoperability was missed by all preoperative staging tests). The sensitivity of CT was poor at 43%. PET and EUS-FNA had similar sensitivity and negative predictive values. However the specificity of EUS-FNA was superior (100% vs. 72% for PET), suggesting that EUS-FNA may be preferred to PET early in staging to identify inoperable patients.

In the three cases presented in this report, EUS-FNA proved to be an invaluable tool in both diagnosing and accurately staging lung cancer. Many patients with suspected lung cancer are smokers, so enlarged mediastinal nodes may indicate infection or other pathologies. Furthermore, common causes of mediastinal lymphadenopathy are co-existent in Asia, including tuberculosis and lymphoma. When used in conjunction with radiographical imaging techniques such as CT, EUS-FNA can perform targeted biopsy of suspicious areas identified radiologically, differentiating them from the non-neoplastic differentials mentioned above.

In expert hands, the sensitivity of EUS-FNA has been shown to reach 90%–98%.[17-19] It also allows access to certain lymph node stations (subcarinal, aortopulmonary window and perioesophageal) that are not easily accessible by mediastinoscopy.[20] Moreover, cancer is ultimately a pathological diagnosis, and EUS-FNA has the added benefit of providing tissue for histological examination, compared to radiographical staging alone. Through the use of EUS-FNA in staging, futile surgery can be avoided, as demonstrated by these three cases. By obtaining tissue for cytological examination, it also guides subsequent chemotherapy, which is based on cell type and molecular markers. Importantly, all three patients recovered uneventfully from the procedure. EUS-FNA is an outpatient procedure that is performed under conscious sedation, unlike mediastinoscopy which requires general anaesthesia and an overnight hospital stay. The reported complication rate of EUS-FNA in large studies is less than 0.5%,[19] and most of these complications were minor. This is in contrast with mediastinoscopy which has a reported complication rate of 2%–5%, including fairly serious complications, such as pneumothorax.[15] Using decision-analysis models, EUS-FNA has been shown to be a cost-effective method of staging lung cancer compared to mediastinoscopy and mediastinotomy.[21]

The future of EUS-FNA lies in several areas: (1) In "CT-negative" patients, EUS-FNA has the ability to detect malignancy in normal-sized lymph nodes. There is some evidence to suggest that it might identify some of the 10% of patients with N2/N3 disease who are not detected by CT or mediastinoscopy.[22,23] (2) In collaboration with endobronchial ultrasonography-guided transbronchial needle aspiration (EBUS-TBNA). EBUS-TBNA has the potential for accurate sampling of lymph nodes and masses in the middle mediastinum and, when combined with EUS-FNA, offers the possibility of minimally invasive staging of the majority of the mediastinum. Both procedures can be undertaken concurrently under conscious sedation.[24] However, experience with EBUS is currently limited. (3) In collaboration with PET, there is growing evidence that PET-positive patients should undergo EUS-FNA due to the high false-positive rate of PET, which may range from 9% to 39%.[25] (4) In conjunction with molecular techniques, the detection of altered gene expression by molecular techniques such as reverse transcriptase polymerase chain reaction, can increase the diagnostic yield of EUS-FNA. (5) In the diagnosis of other conditions such as sarcoidosis, the use of EUS-FNA has been studied in the West.[26] In Asia, it has regional applications, for example, in the diagnosis of TB, particularly in patients from whom sputum cannot be obtained for analysis.

Our experience as well as an extensive review of current literature support the implementation of EUS, with EUS-FNA where appropriate, as a routine procedure in the diagnosis and staging of lung cancer. For certain lymph node stations (subcarinal, aortopulmonary window and perioesophageal), it may replace mediastinoscopy as the gold standard. This obviates the need for more invasive procedures in these cases. The negative predictive value of EUS-FNA, which has been a subject of criticism, can be improved by combining it with EBUS-TBNA to access the anterior mediastinum,[27] or in conjunction with PET.[28]

Unfortunately, the potential of EUS-FNA in lung cancer staging and diagnosis has not been fully realised in Asia, partly as a consequence of the limited number of Asian centres which offer this procedure. The management of lung cancer patients is complex, requiring cooperation between respiratory physicians, thoracic surgeons, radiologists and oncologists. Now that EUS-FNA is emerging as a useful tool in the staging of lung cancer, endoscopists trained in EUS and EUS-FNA will also be able to contribute to the clinical management of the condition. With such a multi-disciplinary approach, steady progress is being made towards an ideal where "extreme remedies" might not be required for an "extreme disease" like lung cancer.

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